

CLAIMS

1. A method for inhibiting a response by a T cell expressing a cell surface receptor which binds a costimulatory molecule, comprising contacting the T cell with an agent which inhibits production of D-3 phosphoinositides in the T cell.
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2. The method of claim 1, wherein the agent is an inhibitor of phosphatidylinositol 3-kinase.
- 10 3. The method of claim 2, wherein the inhibitor of phosphatidylinositol 3-kinase is selected from a group consisting of wortmannin, quercetin and LY294002, and derivatives or analogues thereof.
- 15 4. The method of claim 1, wherein the response by the T cell comprises production of at least one lymphokine.
5. The method of claim 4, wherein the lymphokine is interleukin-2.
- 20 6. The method of claim 1, wherein the response by the T cell comprises proliferation.
7. The method of claim 1, further comprising contacting the T cell with a second agent which inhibits protein tyrosine phosphorylation in the T cell.
- 25 8. The method of claim 7, wherein the second agent is an inhibitor of a protein tyrosine kinase.
9. The method of claim 8, wherein the inhibitor of a protein tyrosine kinase is herbimycin A or a derivative or analogue thereof.
- 30 10. The method of claim 7, wherein the second agent is a tyrosine phosphatase or an activator of a tyrosine phosphatase.
11. The method of claim 10, wherein the tyrosine phosphatase is a cellular tyrosine phosphatase.
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12. The method of claim 11, wherein the cellular tyrosine phosphatase is CD45 or Hcph.

13. The method of claim 12, wherein the second agent is a molecule which binds to and activates CD45.
14. The method of claim 13, wherein the second agent is an anti-CD45 antibody, or
5 fragment thereof.
15. A method for inducing unresponsiveness to an antigen in a T cell expressing a cell surface receptor which binds a costimulatory molecule, comprising contacting the T cell with the antigen and an agent which inhibits production of D-3 phosphoinositides in the T cell.
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16. The method of claim 15, wherein the agent is an inhibitor of phosphatidylinositol 3-kinase.
17. The method of claim 16, wherein the inhibitor of phosphatidylinositol 3-kinase is
15 selected from a group consisting of wortmannin, quercetin and LY294002, and derivatives or analogues thereof.
18. The method of claim 15, wherein the antigen is an alloantigen.
- 20 19. The method of claim 15, wherein the antigen is an autoantigen.
20. The method of claim 15, wherein the T cell is contacted with the antigen and the agent *in vitro* and the method further comprises administering the T cell to a subject.
- 25 21. A method of claim 20, wherein the antigen is on a surface of an allogeneic or xenogeneic cell and the subject is a recipient of an allogeneic or xenogeneic cell.
22. A method of claim 20, wherein the subject is suffering from an autoimmune disease or a disorder associated with an inappropriate or abnormal immune response.
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23. A method for stimulating a response by a T cell which has received a primary activation signal and expresses a surface receptor that binds a costimulatory molecule, comprising contacting the T cell with an agent which stimulates production of D-3 phosphoinositides in the T cell.
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24. The method of claim 23, wherein the agent is an activator of phosphatidylinositol 3-kinase.

25. The method of claim 23, wherein the response by the T cell comprises production of at least one lymphokine.
- 5 26. The method of claim 25, wherein the lymphokine is interleukin-2.
27. The method of claim 23, wherein the response by the T cell comprises proliferation.
28. The method of claim 23, further comprising contacting the T cell with a second agent
10 which stimulates protein tyrosine phosphorylation in the T cell.
29. The method of claim 28, wherein the second agent is an activator of a protein tyrosine kinase.
- 15 30. The method of claim 28, wherein the second agent is an inhibitor of a cellular tyrosine phosphatase.
31. The method of claim 30, wherein the cellular tyrosine phosphatase is CD45.
- 20 32. A method for stimulating a response to an antigen by a T cell expressing a cell surface receptor which binds a costimulatory molecule comprising contacting the T cell with the antigen and an agent which stimulates production of D-3 phosphoinositides in the T cell.
33. The method of claim 32, wherein the agent is an activator of phosphatidylinositol 3-
25 kinase.
34. The method of claim 32, wherein the antigen is a tumor-associated antigen.
35. The method of claim 32, wherein the antigen is from a pathogen selected from the
30 group consisting of a bacteria, a virus, a fungus and a parasite.
36. The method of claim 32, wherein the T cell is contacted with the antigen and the agent *in vitro* and the method further comprises administering the T cell to a subject.
- 35 37. A method of claim 36, wherein the antigen is expressed by a tumor cell present in the subject.

38. A method of claim 36, wherein the antigen is expressed by a pathogen present in the subject.

39. A method for identifying an inhibitor of a phosphatidylinositol 3-kinase comprising:

- a) providing a T cell which expresses a receptor that binds a costimulatory molecule;
- b) stimulating an intracellular signal transduction pathway in the T cell associated
- 5 with ligation of the receptor in the presence of an agent to be tested; and
- c) determining an amount of at least one D-3 phosphoinositide produced in the T cell,

wherein a reduced amount of at least one D-3 phosphoinositide produced in the T cell in the presence of the agent relative to an amount produced in the T cell in the absence of the agent

10 indicates that the agent is an inhibitor of a phosphatidylinositol 3-kinase.

40. The method of claim 39, wherein the receptor is CD28.

41. The method of claim 40, wherein the T cell is contacted with a ligand for CD28.

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42. The method of claim 40, wherein the ligand for CD28 is a membrane-bound form of a B lymphocyte activation antigen selected from the group consisting of B7-1 and B7-2.

43. The method of claim 39, wherein production of at least one D-3 phosphoinositide in the T cell is measured by high pressure liquid chromatography.

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44. A method for identifying an activator of phosphatidylinositol 3-kinase comprising:

- a) contacting a T cell which expresses a receptor that binds a costimulatory molecule
- 25 with an agent to be tested; and
- b) determining an amount of at least one D-3 phosphoinositide produced in the T cell,

wherein an increased amount of at least one D-3 phosphoinositide produced in the T cell in the presence of the agent relative to an amount produced in the T cell in the absence of the agent indicates that the agent is an activator of a phosphatidylinositol 3-kinase.

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45. The method of claim 44, wherein production of at least one D-3 phosphoinositide in the T cell is measured by high pressure liquid chromatography.

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